Randomized comparison of bleeding patterns in women using a combined contraceptive vaginal ring or a low-dose combined oral contraceptive on a menstrually signaled regimen

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Abstract: OBJECTIVES: To compare bleeding patterns for 12months continuous use of a contraceptive ring [contraceptive vaginal ring (CVR)] and pill [combined oral contraceptive (COC)] on a menstrually signaled regimen and the effectiveness of 4days "treatment withdrawal" to stop bleeding. STUDY DESIGN: Women, 66 to each group, were randomized to continuous use of a CVR (15mcg ethinyl estradiol/150mcg etonogestrel) or a low-dose pill (20mcg ethinyl estradiol/100mcg levonorgestrel) for 360days on a menstrually signaled regimen. Bleeding/spotting days, daily use of ring or pill, was recorded. Endpoint was the total number of bleeding/spotting days for each method over four 90-day reference periods (RP) plus the analysis of bleeding patterns using modified World Health Organization criteria. RESULTS: There was a reduction in the mean (±S.D.) number of bleeding/spotting days from RP1 (CVR 14.2±10; pill 16.6±10.9) to RP4 (CVR 8.8±9.6; pill 8.8±9.1). Fifteen percent of CVR and 4% COC users experienced amenorrhea or infrequent bleeding throughout the study. Amenorrhea increased over time (RP1 vs. RP4: CVR 10% vs. 21% and COC 2% vs. 30%). Compliance with the menstrually signaled regimen was poor. Ceasing hormones for 4days stopped a bleeding episode within 5days in the majority of episodes and many stopped spontaneously. CONCLUSION: Bleeding patterns with continuous use of the CVR and COC are similar and improve over 1year of use. The unpredictability, but short duration, of bleeding episodes should be stressed during counseling. IMPLICATION: This information for clinicians and women about breakthrough bleeding patterns with use of a CVR or combined pill over 12months using a menstrually signaled regimen will give women an indication of what to expect with continuous use.

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Randomized comparison of bleeding patterns in women using a combined contraceptive vaginal ring or a low-dose combined oral contraceptive on a menstrually signaled regimen☆,☆☆

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Abstract

Objectives: To compare bleeding patterns for 12 months continuous use of a contraceptive ring [contraceptive vaginal ring (CVR)] and pill [combined oral contraceptive (COC)] on a menstrually signaled regimen and the effectiveness of 4 days "treatment withdrawal" to stop bleeding.

Study design: Women, 66 to each group, were randomized to continuous use of a CVR (15 mcg ethinyl estradiol/150 mcg etonogestrel) or a low-dose pill (20 mcg ethinyl estradiol/100 mcg levonorgestrel) for 360 days on a menstrually signaled regimen. Bleeding/spotting days, daily use of ring or pill, was recorded. Endpoint was the total number of bleeding/spotting days for each method over four 90-day reference periods (RP) plus the analysis of bleeding patterns using modified World Health Organization criteria.

Results: There was a reduction in the mean (±S.D.) number of bleeding/spotting days from RP1 (CVR 14.2±10; pill 16.6±10.9) to RP4 (CVR 8.8±9.6; pill 8.8±9.1). Fifteen percent of CVR and 4% COC users experienced amenorrhea or infrequent bleeding throughout the study. Amenorrhea increased over time (RP1 vs. RP4: CVR 10% vs. 21% and COC 2% vs. 30%). Compliance with the menstrually signaled regimen was poor. Ceasing hormones for 4 days stopped a bleeding episode within 5 days in the majority of episodes and many stopped spontaneously.

Conclusion: Bleeding patterns with continuous use of the CVR and COC are similar and improve over 1 year of use. The unpredictability, but short duration, of bleeding episodes should be stressed during counseling.

Implication: This information for clinicians and women about breakthrough bleeding patterns with use of a CVR or combined pill over 12 months using a menstrually signaled regimen will give women an indication of what to expect with continuous use.

Keywords: Compliance; Frequent bleeding/spotting; Duration; Convenience

1. Introduction

A large global survey in 2012 found that 50% of women wanted flexibility to determine when their menstruation would start, with 36% wanting not to bleed at all or only once every 2–3 months, while for 44%, regular bleeding was important [1]. Other surveys have shown that 30–50% prefer amenorrhea, 40% prefer to bleed 2–4 times a year and 40% want regular monthly menses [2,3]. An 8-country survey found that 58% of women would accept irregular bleeding initially if they had fewer periods over time [4].

A number of studies have looked at extended use of combined oral contraceptives (COCs) and NuvaRing,

☆ Declaration of interest: The CVRs used in the study were provided by MSD and the COC was provided by Bayer Healthcare. Neither company was involved in any aspect of the design, execution or analysis of results. Edith Weisberg has provided expert opinion for MSD and Bayer Healthcare, has been supported to attend conferences by Bayer Healthcare and has obtained research funding for investigator-initiated research from both companies. Gabriele Susanne Merki-Feld has financial relationships (as a lecturer, member of advisory boards and/or consultant) with MSD and Bayer-Schering Pharma, AG. Ian Fraser has been a member of Advisory Boards and given sponsored lectures for Bayer Healthcare, MSD, Daiichi-Sankyo and Vifor Pharma, and has received occasional research funding from these companies.

☆☆ Clinical trial registration ACTRN12609000391279.

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mainly for 84 or 91 days [5,6]. A 12-month randomized study in American women compared the bleeding profile of a flexible extended regimen of ethinylestradiol/drospirenone with the standard 24/4 day regimen [7]. Although two other studies compared scheduled 3- or 4-day hormone-free intervals in women using 6 months continuous combined hormonal contraception [8,9], none addressed "menstrually signaled" regimens and no studies provide a detailed analysis of such regimens or a made a comparison between different delivery programs for combined hormonal contraceptives.

We report on a detailed analysis of bleeding patterns in women randomly assigned to 12 months continuous use of a vaginal ring [contraceptive vaginal ring (CVR)] or a low-dose COC on a menstrually signaled regimen.

In this study, our primary comparison was focused on the number of bleeding or spotting days between women using a combined CVR releasing 15 mcg ethinyl estradiol and 150 mcg etonogestrel daily vs. a COC containing 20 mcg ethinyl estradiol and 100 mcg levonorgestrel continuously over 12 months on a menstrually signaled regimen that required women to remove the CVR or stop their pill on the fifth day if a bleeding/spotting episode persisted beyond 4 days and to restart after a 4-day interval. We also compared the acceptability of and women's satisfaction with the two treatments and the impact of 4 days cessation of treatment on bleeding episodes irrespective of mode of administration.

2. Methods and materials

Women aged between 18 and 45 years requesting contraception were recruited through Family Planning New South Wales clinics in Sydney, Australia, the telephone information service, the Research Centre database and Facebook advertisements. Women with no contraindications who were willing to use hormonal contraception continuously for 12 months and maintain a menstrual diary were enrolled after giving informed consent. Women could be new users, restarters or switchers and they needed to accept randomization. Exclusion criteria were current pregnancy, undiagnosed intermenstrual bleeding, body mass index of >30 kg/m^2, risk factors or history of thromboembolism or cardiovascular disease, blood pressure of $>149/90$ mmHg, smokers aged ≥ 35 years, current users of enzyme inducing drugs or users of injectable contraception within the last 6 months.

At the screening visit, women completed a menstrual attitudes questionnaire, based on the "ARHP Menstrual Attitudes Questionnaire" [10] including their preference for frequency of menses. A physical examination including vital signs and gynecological examination were performed and a Pap smear was taken, if there was no smear within the past 2 years.

Eligible women were randomized according to a computer-determined scheme to either continuous CVR use with replacement of a new ring every 28 days or daily active COC pill ingestion. The allocation, contained in a consecutively numbered sealed opaque envelope, was opened by the subject at the randomization visit. The women inserted the ring or started the pill on the first day of their next period and completed a daily paper diary to record whether the ring was in situ or a pill was taken and any bleeding/spotting occurred. If a bleeding/spotting episode recurred within 14 days of a previous break in contraceptive use, women were asked to contact the research coordinator for further instructions. Participants were seen at the Research Centre 2, 4, 6 and 12 months after starting their medication. The research coordinator telephoned participants at 1, 3 and 5 months to ensure that they were completing the daily diary and correctly following instructions for ceasing medication if a bleeding/spotting episode exceeded 4 days.

At each clinic visit, menstrual diaries were checked for compliance and clarification, and weight and vital signs were checked. At conclusion or withdrawal, physical and gynecological examinations were again carried out. The menstrual questionnaire was readministered.

The primary outcome for the study was the difference in mean number of bleeding/spotting days between the groups over time. Secondary outcomes were the proportion of women who reported a particular bleeding pattern and the number of days it took for a bleeding episode to stop following cessation of hormones.

The power calculation indicated that 70 women would be required for each arm to detect a difference of 0.5 standard deviations in our primary outcome (mean number of days of bleeding/spotting) with 90% power and significance level of 0.05.

Bleeding/spotting episodes and duration were analyzed in four 90-day reference periods (RP). For each RP, the number of bleeding/spotting days combined and separately was calculated for each subject according to group assignment. The mean number of bleeding/spotting days was then compared between groups and over time. For each individual, the bleeding diary was converted to an Excel graph for visual comparison of bleeding patterns. The bleeding patterns for each RP were also assessed according to World Health Organization (WHO) criteria [11]. We calculated the percentage of women who reported a particular bleeding pattern.

The analysis was carried out using the SAS 9.3 program.

The study was approved by the Family Planning New South Wales Ethics Committee, and fully informed consent was obtained. The clinical trial was registered (ACTRN12609000391279).

3. Results

Of 144 women screened, 5 were screen failures and 7 withdrew before randomization (Fig. 1). Sixty-six women were assigned to each method. One woman in each group

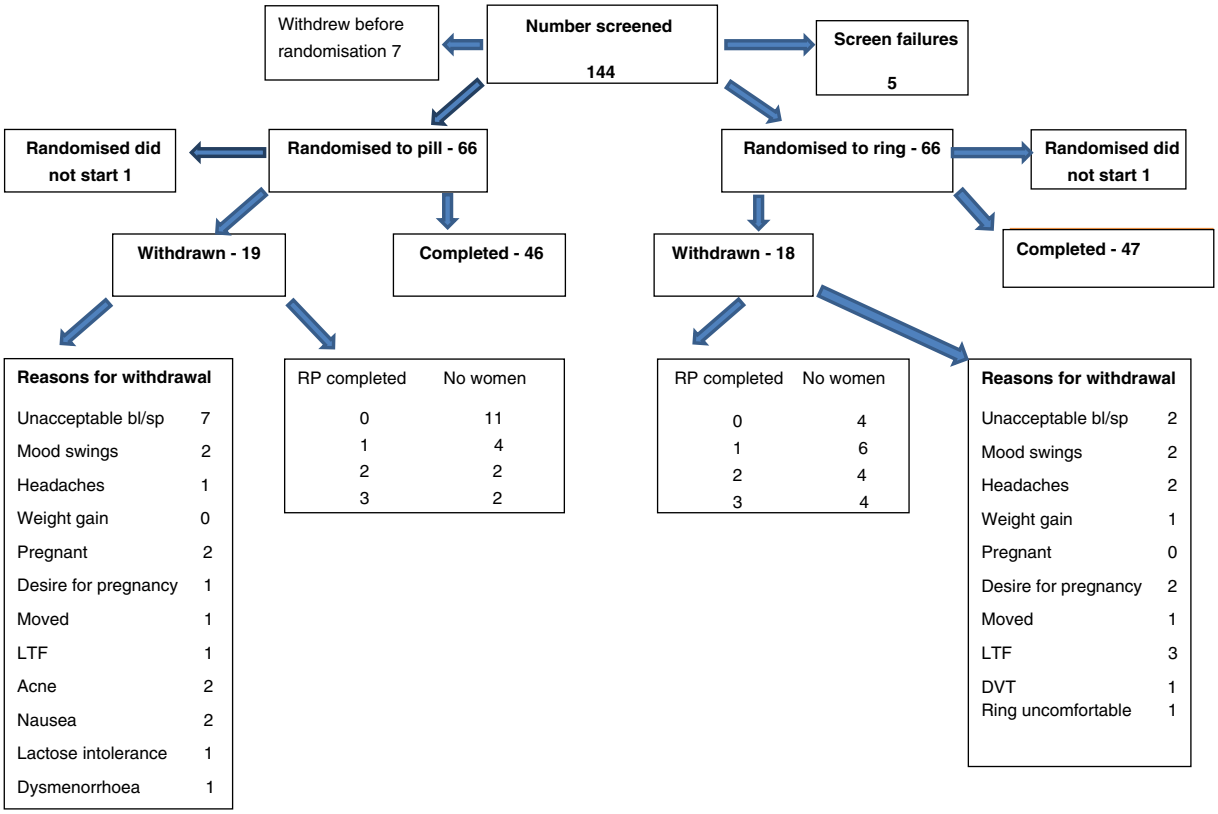

Fig. 1. Study flow chart.

withdrew before starting the medication (Fig. 1). Demographic characteristics of the participants are demonstrated in Table 1.

Among women using the COC, 26 admitted to missing at least one pill, mainly in RP1 and RP2. In most instances (71%), this did not result in breakthrough bleeding (BTB) but occasionally resulted in 1–3 days of spotting, which stopped spontaneously irrespective of RP. Missing a pill 2 or 3 times in a single RP did not appear to provoke BTB. Women missing consecutive pills were more likely to bleed but stopped spontaneously within 2–3 days. The CVR was expelled in two users, one started bleeding immediately in RP2, while the other was uncertain how long the ring had been out but she did not bleed. Six women removed their ring for 1 day at different times but did not have BTB, although one woman who removed her ring for 2 days in RP4 bled for 3 days.

We found little difference in the mean number of days of bleeding/spotting per RP between the two groups (p=.27) (Fig. 2). However, the mean number of days decreased from RP1 to RP4 for both methods (16–9 days for the CVR, and 14–9 days for the COC; p<.001). Similar results were found for these two comparisons for bleeding only (p=.55 and p<.001), spotting only (p=.26 and p<.001) and number of episodes (p=.30 and p<.001), a trend already apparent at RP2 (Table 2).

Adherence to the menstrually signaled regimen was inconsistent based on diaries, with women complying precisely with instructions for stopping medication after 4 days of bleeding in only 42% of episodes. Overall, in compliant episodes, 50% of women had ceased bleeding/spotting by 4 days after stopping medication and 91% had

Table 1
Demographics of participants.

		COC (*n*=54)	CVR (*n*=61)
		n (%)	*n* (%)
Age group	<20	6 (11)	6 (10)
	20–24	24 (44)	22 (36)
	25–29	15 (28)	20 (33)
	30–4	6 (11)	6 (10)
	≥35	3 (6)	7 (11)
Highest level of education	Secondary	10 (19)	10 (16)
	Technical/ vocational	9 (17)	12 (20)
	University	35 (65)	39 (64)
Cultural background	Caucasian	40 (74)	52 (85)
	Other	14 (26)	9 (15)
Total number of pregnancies	0	40 (74)	45 (74)
	1	5 (9)	5 (8)
	≥2	9 (17)	11 (18)
Number of living children[a]	0	46 (85)	51 (85)
	1	2 (4)	1 (2)
	≥2	6 (11)	8 (13)

[a] Information missing for one woman in CVR group.

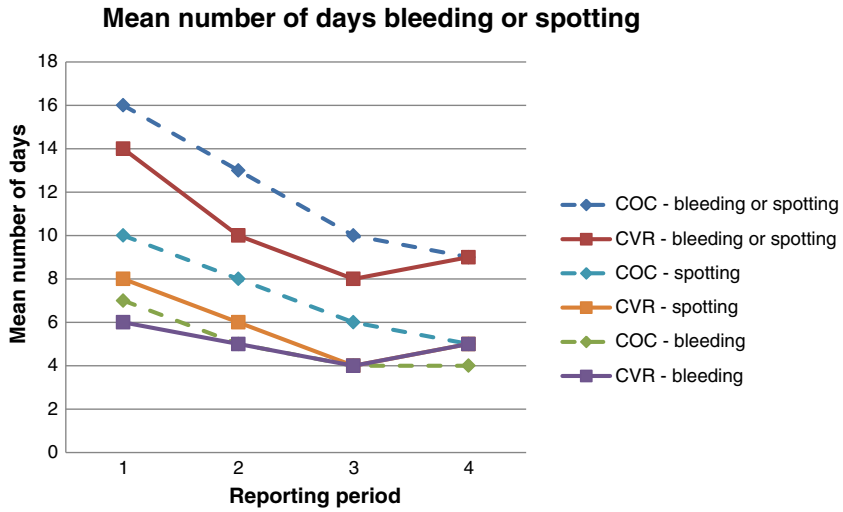

Fig. 2. Mean number of bleeding/spotting days according to RP for women allocated to CVR or COC.

ceased by 7 days after stopping (and restarting). Of 73 episodes of bleeding/spotting, which stopped spontaneously, 46 (63%) lasted 4 days or less and 26 (35%) stopped between 5 and 8 days. None lasted longer than 8 days (Table 3).

Nine women withdrew because of unacceptable bleeding patterns: 5 COC users before completing RP1 and 2 after completing RP2; 1 CVR user after RP1 and 1 after RP3. Other reasons for premature withdrawal were similar to those reported in other combined hormonal contraceptive studies (Fig. 1).

When the data were analyzed using the WHO criteria [11], a higher proportion of COC users had frequent bleeding while a higher proportion of CVR users had more infrequent bleeding (Table 3).

When asked at completion or early withdrawal from the study, the majority of women preferred continuous use of hormonal contraception: 41 (93%) CVR users and 42 (84%) COC users. The majority of women [60 (73%)] were very satisfied or somewhat satisfied [13 (14%)] with the regimen. The major reasons for liking continuous use were ease of use and infrequent or no bleeding. No period pain, headaches or premenstrual syndrome were also advantages for some women. The unpredictability of bleeding was the factor most disliked by half the women who were otherwise happy with the regimen.

Table 2
The number of days elapsed for bleeding/spotting to stop after ceasing hormonal contraceptive medication for 4 days.

Number days to stop bleeding after stopping medication	Number of episodes	Percentage (%)	Cumulative percentage (%)
0[a]	83	17	
1	16	3	
2	24	5	
3	38	8	
4	84	17	50
5	101	21	71
6	73	15	
7	31	6	92
8	22	5	
9	8	2	
10	7	1	
11	3	1	
12	0		
13	0		
14	1	0.2	100

[a] Ceased at time they stopped medication.

4. Discussion

The current study randomly compares two delivery methods of combined hormonal contraception used on a menstrually signaled regimen over 12 months. It reports on bleeding/spotting days and also bleeding episodes and patterns according to the modified WHO criteria.

The vaginal bleeding patterns associated with continuous estrogen–progestogen or progestogen-alone contraceptive regimens are quite different from spontaneous cyclical menstrual patterns and have required new approaches to description and analysis. Initial discussions on such a concept began in the early 1970s [12]. WHO sponsored a major international study in 10 developing and developed countries [13], taking into account the patient perception of experienced patterns, including duration and variation in flow — the "comfort" factors in bleeding experience.

A significant later contribution of this program was the development of a series of "clinically relevant bleeding patterns" determined from the appeal and tolerance of particular bleeding patterns by women in large-scale WHO clinical trials. The program also assessed menstrual patterns in a very large database of untreated women and refined their analysis and definitions of clinically relevant bleeding patterns based on these data [11].

More recently, Mishell and colleagues have drawn attention to the continuing need for a uniform approach to

Table 3
Percentage of women with different bleeding patterns per 90-day RP according to CVR or COC use.

	CVR	COC	CVR	COC	CVR	COC	CVR	COC
	RP1	RP1	RP2	RP2	RP3	RP3	RP4	RP4
	No %	No %	No %	No %	No %	No %	No %	No %
Frequent bleeding, 4 episodes	1 (2)	3 (6)	0	3 (6)	0	2 (4)	0	0
Infrequent bleeding, <2 episodes	14 (23)	10 (19)	18 (37)	14 (28)	14 (29)	7 (15)	15 (32)	6 (13)
No bleeding	6 (10)	1 (2)	7 (13)	4 (8)	17 (35)	12 (25)	10 (21)	14 (30)
Prolonged bleeding, ≥10 days	21 (34)	21 (39)	19 (39)	11 (22)	8 (16)	3 (2)	15 (32)	6 (13)
Irregular bleeding, range of lengths of bleeding-free intervals exceeding >17 days	3 (5)	2 (4)	3 (6)	3 (6)	2 (4)	4 (8)	0	2 (4)

descriptions and analysis of bleeding patterns in women using hormonal contraceptive preparations [14,15]. The International Federation of Gynecology and Obstetrics (FIGO) has established a FIGO Menstrual Disorders Standing Committee who have strongly recommended new and uniform approaches to nomenclature and definitions around normal and spontaneously abnormal uterine bleeding [16]. Hence, it is clear that there are still issues around the description of bleeding patterns that remain to be addressed, especially in terms of community perception and women's comfort and tolerance of particular patterns. However, the currently endorsed international approach does allow valuable, hard, scientific comparison of basically unpredictable and highly variable patterns of moderate bleeding and very light bleeding ("spotting") in groups of women using differing hormonal contraceptive preparations.

Such detailed analyses can support doctors in counseling women about what to expect when they start continuous regimens.

Although individual bleeding patterns were variable and unpredictable for both methods, the mean number of bleeding/spotting, bleeding or spotting days and number of episodes were similar for the two methods, although there was a significant decrease for all these parameters between RP1 and RP4 for both. This could be due, in part, to women with more problematic bleeding withdrawing from the study, although study of individual patterns does not support this. It also confirms experience from other studies that, over time, bleeding patterns in women using continuous hormonal contraception improve substantially [7–9].

There appeared to be subtle differences in bleeding patterns between the two methods. CVR users experienced more RPs with no bleeding and more RPs with infrequent but prolonged bleeding, whereas COC users tended to have more RPs with short-light spotting episodes (Table 3).

Surveys indicate that approximately 36% of women in many countries do not want to bleed at all or only once every 2 or 3 months [1,2]. In our study, 44% preferred no bleeding at all. What is important to many women is how manageable their bleeding is, impinging as little as possible on daily activities and quality of life. The majority of women prefer to have fewer bleeding days and less heavy bleeding [1,2,17]. Only 37% wanted monthly bleeding [18]. Around 30% of women feel that menstrual bleeding has a severe negative impact on their daily life [2,17]. In a recent Swiss survey, 80% of the participants wanted fewer bleeding days while using a contraceptive [18].

Although compliance with the regimen of stopping medication for 4 days on the fifth day of a bleeding/spotting episode was inconsistent, an episode persisting for more than 4 days was likely to stop spontaneously for many women within a reasonable time (4–8 days). Among women who stopped their combined hormonal contraceptive for 4 days, two thirds of bleeding/spotting episodes stopped within the next 5 days, useful information for women wishing to use continuous combined methods.

This was an open-label randomized study with two well-matched groups. The research coordinator was in monthly contact with the subjects to encourage completion of the menstrual diary. Although the study relied on self-reporting, it is likely that this regular contact ensured a reasonably accurate completion of the menstrual diaries, providing reliable data on bleeding patterns. It is possible that using a higher-dose COC may have provided better cycle control but we decided on a 20EE/100LNG COC to make it reasonably comparable in ethinyl estradiol serum levels to those achieved with the CVR [11].

The bleeding pattern with extended regimens may vary with estrogen and progestogen dosage and delivery route [17]. Most studies demonstrate that the total number of bleeding days with extended hormonal contraceptive cycles decreases over time. However, the high rate of unscheduled, albeit light, bleeding compromises this advantage and may be a cause for the often high dropout rate [4,6,11,16,18]. In menstrually signaled regimens, recommending a break varying between 3 and 7 days to stop longer bleeding episodes [11,16], dropout rates are high even though these regimens result in fewer bleeding days. The large number of women using these regimens, who were not compliant in our and other studies, indicate that detailed counseling is needed.

In this study, the number of baseline bleeding/spotting days and their decrease over the four RP with the 20EE/100LNG pill were in the range observed in other studies with 20 and 30 mcg ethinyl estradiol/levonorgestrel combinations in 84/7 nonsignaled regimens [7–9]. The high dropout rate of more than 40% in 84/7 studies may have biased the low

number of bleeding/spotting days reported in these trials. Our finding that a 4-day break in hormone use stops bleeding in two thirds of episodes within 5 days may be helpful in increasing continuation rates, especially during the initial months. The goal of most women participating in extended cycle regimens is a desire to achieve amenorrhea. After 1 year, continuous use of a 20 mcg ethinyl estradiol/100 mcg levonorgestrel COC Miller reported amenorrhea during RP4 in 72% of users [18]. In our study, the rate of amenorrhea was much lower with both study preparations. However, the sum of amenorrhea and infrequent bleeding, both convenient bleeding patterns, was around 60% for both the ring and the pill.

5. Conclusion

This study provides information on bleeding patterns to be expected using these regimens. Continuous CVR use appears to result in infrequent but prolonged bleeds every 2–3 months while continuous low-dose COC use appears to produce more frequent, but shorter spotting episodes.

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